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Tetrahedron Letters 47 (2006) 3843–3847
Tetrahedron Letters

β-Homoamino acids as catalysts in enantioselective intra- and intermolecular aldol reactions

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Received 28 February 2006; revised 23 March 2006; accepted 29 March 2006
Available online 27 April 2006

Abstract—β^3-Homoamino acids catalyze the intra- (cf. the Hajos–Parrish–Eder–Sauer–Wiechert reaction) as well as the intermolecular aldol reaction. The stereochemical outcome with selectivities of up to 83% ee is reversed in the intramolecular reaction, when we go from the proteinogenic amino acids to the homologues, and reaction time increases dramatically for both reactions. In contrast, in the intermolecular reaction Me-β^3hPhe-OH gives the same enantiomer as (*S*)-proline does, but with lower enantiomeric excess (54% vs 48% ee).

1. Introduction

The simple amino acid proline is an outstanding and versatile catalyst in asymmetric intra- and intermolecular aldol reactions.[1] Surprisingly, its synthetic potential has been forgotten for nearly 30 years (cf. the Hajos–Parrish–Eder–Sauer–Wiechert reaction[2]). Other amino acids have received scant attention as organocatalysts, for example, alanine in the intermolecular aldol reaction,[3] although Hajos and Parrish,[2a] as well as Eder et al.,[2b] used phenylalanine in the first organocatalytic intramolecular aldol condensation of achiral triones (later known as so-called Shibasaki-conditions).[4] It is equally surprising that as early as in 1977, that is a few years after the groundbreaking results of Eder et al. (at Schering, Berlin, Germany)[2b] and Hajos and Parrish (at Roche, Nutley, USA),[2a] the group around Buchschacher (Roche, Basel, Switzerland) reported, β-amino acids, such as β^3-homoproline, β^3-homophenylalanine and also γ-amino acids are effective catalysts in intramolecular asymmetric aldol condensations![5] These findings have not been recognized either, until β^3-homoamino acids were 're-invented' as organocatalysts in 2004/05: Whereas β^3-homoproline is ineffective in the Michael addition of ketones to nitrostyrenes,[6] the cyclic β-amino acid (1*R*,2*S*)-cispentacin (Fig. 1) has now been reported to be almost as effective as proline in the Hajos–Parrish–Eder–Sauer–Wiechert reaction (94 vs >99% yield, 90 vs 93% ee at 30 mol % amino acid).[7]

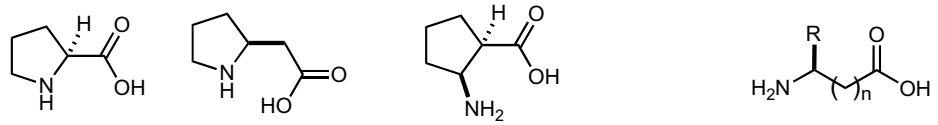

Figure 1. Amino-acid derivatives used in the asymmetric catalytic intra- and intermolecular aldol reaction.

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doi:10.1016/j.tetlet.2006.03.183

This 'renaissance' encouraged us to explore the potential of various β^3-homoamino acids as organocatalysts in an intra- and an intermolecular aldol reaction.

2. Intramolecular aldol reaction

The application of various β^3-homoamino acids (20 mol %) in the intramolcular aldol condensation of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (**1**) to (−)-(7a*R*)-7a-methyl-2,3,7,7a-tetrahydro-1*H*-indene-1,5-(6*H*)-dione (**2**) under the conditions of Hajos and Parrish,[8] but at slightly higher temperature (20 vs 16 °C), generally requires longer reaction times (4 d vs 20 h), as compared to proline (Scheme 1 and Table 1). Although, even at 3 mol % of proline for this reaction an enantiomeric excess of 93% is reported (20 h, DMF),[2a] under our conditions (20 mol %, 4 d, DMF) **2** is formed with 76% ee at the best. It should be mentioned that small amounts of water do not only increase the reaction rate, but also decrease the stereoselectivity of the reaction.[9] Of the tested α-amino acids, proline and phenylalanine were the only ones to give (*S*)-**2** within 1–16 d, whereas the reaction with valine and alanine was significantly slower.

Interestingly, all investigated β^3-amino acids yielded (*R*)-**2**, that is the enantiomer of the bicyclic compound obtained in excess with α- and with γ-amino acids as catalysts with good selectivity (52–83% ee). This reverse of stereoselectivity seems to be a general trend for β-amino acids.[5,7]

Although for proline and primary α-amino acids a carboxylic acid-catalyzed enamine mechanism is generally accepted,[10] and the significant drop of enantioselectivity by using the latter is attributed to the increased conformational flexibility of primary amino acids by quantum mechanical studies,[10c] an explanation for the reversed stereoselectivity of β-amino acids is still elusive.

Of the β-amino acids, those with aliphatic side chains (H-β^3hAla-OH, H-β^3hIle-OH, H-β^3hLeu-OH) gave (*R*)-**2** in moderate yields (29–54%) but with surprisingly good enantioselectivities (75–83% ee). This is especially remarkable, since under the same conditions (DMF, 4 d, 20 °C) the insoluble alanine and valine gave **2** in less than 5% yield and even proline led to (*S*)-**2** of 76% ee in 85% yield. Use of a soluble *p*-methoxyanilide derivative of the insoluble H-β^3hIle-OH, a trick also known for proline,[11] leads to a homogeneous reaction mixture, but after 10 d only starting material **1** was recovered.

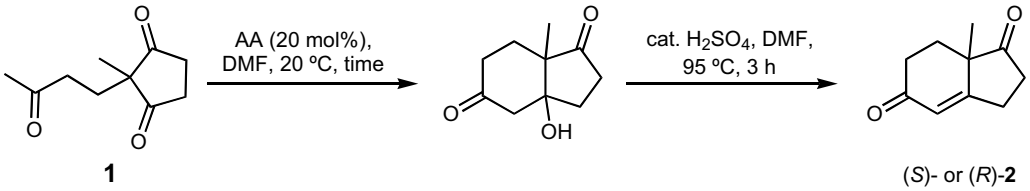
β-Homoamino acids with aromatic side chains, such as H-β^3hTrp-OH and H-β^3hPhe-OH, gave (*R*)-**2** in better yields than those with aliphatic side chains (up to 65%), but with lower enantioselectivites (52–75% ee). Yield increased by use of 30 mol % of H-β^3hPhe-OH, whereas the ee rose only slightly (64% yield, 75% ee vs 86% yield, 77% ee). With Me-β^3hPhe-OH the reaction time decreased dramatically (from 4 to 1 d!) and (*R*)-**3** was obtained in 56% yield, but in almost racemic form.

3. Intermolecular aldol reaction

In the proline-catalyzed reaction of acetone with *p*-nitrobenzaldehyde (**3**) the aldol (*R*)-**4** is formed in 65% yield and 54% ee within 1 d.[1a] Amongst all non-cyclic α-amino acids, only valine has shown potential in this reaction (in the presence of 1 mol % of water) to give the aldol (*R*)-**4**, along with 42% of **5**, within 3 d in 50% yield and 72% ee, at best.[12] Furthermore, other α-amino acids, such as histidine, tyrosine, phenylalanine and Me-Val-OH gave **4** in less than 5% yield.[1a] Surprisingly none of the β-homologues has been tested in this reaction.

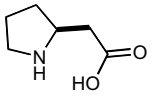
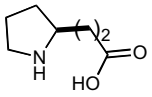
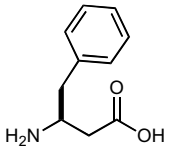
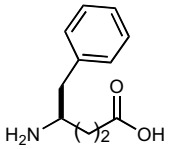
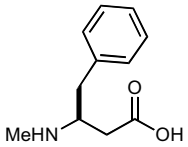
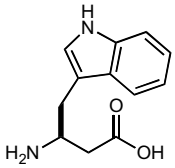
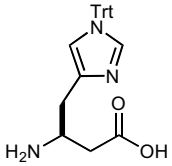
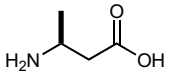
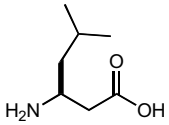
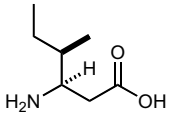
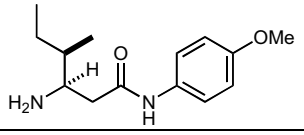
In our hands, under the standard-conditions (DMSO, 20 °C, 22 d, 20 mol % catalyst) none of the tested amino acids led to formation of aldol **4** with yields higher than 5%, in the absence or presence of 1 mol % of water[12] (Scheme 2 and Table 2). Amazingly, the secondary amine Me-β^3hPhe-OH, which was not selective at all in the intramolecular reaction, caused formation of (*R*)-**4** with 48% ee in 58% yield within 3 d, besides **5** (ratio **4**/**5** = 3.34:1). Here, the steric course of the reaction is the same, as compared to proline as catalyst.

In summary, we have shown that especially β^3-homoamino acids with aliphatic side chains give enantioselectivities similar to proline in the intramolecular aldol condensation, albeit it must be pointed out that they are much more expensive. The stereochemical outcome with selectivities of up to 83% ee is reversed in the intra- but not in the intermolecular aldol reaction, when we go from the proteinogenic amino acids to their homologues.



Scheme 1. β^3-Amino acids in the intramolecular aldol condensation.

Table 1. Catalyst screening for the intramolecular aldol condensation

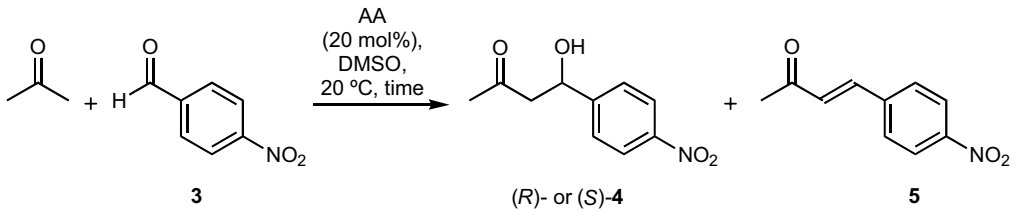
Amino acid (AA)		Time (d)	Yield **2**[a] (%)	ee[b] (%)
H-Val-OH, H-Ala-OH	het.[c]	10	<5	n.d.[d]
H-Pro-OH	hom.	4	85	76 (*S*)
	n.d.[6]	13	99	58 (*R*)
	n.d.[6]	22	47	7 (*S*)
H-Phe-OH	het.[6]	16	85	25 (*S*)
	hom.	4	64	75 (*R*)
	n.d.[6]	20	65	42 (*R*)
	het.	1	56	0
	het.	4	65	52 (*R*)
	hom.	4	<5	n.d.[c]
	het.	4	49	78 (*R*)
	hom.	4	29	83 (*R*)
	het.	4	54	75 (*R*)
	hom.	10	<5	n.d.[c]

[a] Yield after flash column chromatography.

[b] Determined by HPLC on a Chiralpak AD-H (0.46 × 25 cm). Flow 1 mL/min, $\lambda = 254$ nm, hexane/*i*PrOH = 50:1. t_R (*S*) = 24.3 min, t_R (*R*) = 25.8 min.

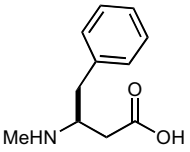
[c] Het. and hom. indicates whether the reaction mixtures are heterogeneous or homogeneous.

[d] Not determined.



Scheme 2. β^3-Homoamino acids in the intermolecular aldol reaction of acetone with *p*-nitrobenzaldehyde.

Table 2. Catalyst screening in the intermolecular aldol-reaction of acetone with *p*-nitrobenzaldehyde

Amino acid (AA)	Time (d)	Yield **4**[a] (%)	ee[b] (%)	Ratio **4**/**5**[c]
H-Pro-OH	3	65 (hom.)	54 (*R*)	6.23:1
H-(*R*)-Pro-OH	3	48 (hom.)	76 (*S*)	1.03:1
H-Val-OH	3	50 (hom.)	72 (*R*)[d]	1.19:1
H-Ala-OH, H-Phe-OH, H-β^3hAla-OH, H-β^3hIle-OH, H-β^3hPhe-OH, H-β^3hTrp-OH, H-β^3hHis(Trt)-OH	22	<5 (hom.)	n.d.[e]	—
	3	58 (hom.)	48 (*R*)	3.34:1

[a] Isolated yield after flash column chromatography.
[b] Determined by HPLC on a Chiralcel OJ (0.46 × 25 cm). Flow 1 mL/min, $\lambda = 254$ nm, hexane/*i*PrOH = 9:1. t_R (*R*) = 28.2 min, t_R (*S*) = 31.5 min.
[c] Determined from the crude ^{1}H NMR spectrum.
[d] In the presence of 1 mol % water.
[e] Not determined.

Acknowledgements

M.L. gratefully acknowledges fellowships from the German Merit Foundation (Studienstiftung des Deutschen Volkes) during undergraduate (2000–2002) and graduate studies (2002–2004). Novartis Pharma AG, CH-Basel, is thanked for financial support. M.L. is grateful to Professor D. Seebach, ETH Zürich, for fruitful discussions and proofreading of the manuscript and Professor E. M. Carreira for sharing HPLC facilities.

Supplementary data

Experimental procedures, characterization data and chromatographic analyses of enantiomerically enriched products. This material is available free of charge via the Internet at http://www.sciencedirect.com. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.183.

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